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A7

30. (Amended) The fusion protein of claim 28, wherein the second peptide portion comprises HBNF or MK, or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or a combination thereof.

31. (Amended) The fusion protein of claim 30, wherein the second peptide portion comprises an N-terminal truncated form of HBNF or MK including at least about 60% of the wild-type HBNF or MK amino acid sequence.

A8

43. (Amended) A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis, bone growth, wound healing, or any combination thereof, wherein the VEGF peptide portion is at least about 115 amino acids in length and the second peptide portion lacks a collagen binding domain.

Please cancel claims 10, 11, 14, 15, 29, and 42.

REMARKS

Information Disclosure Statement

Applicants respectfully request confirmation of the consideration of the references identified in the Information Disclosure Statements dated September 21, 2001 and July 31, 2002 (references DY and DZ), by providing applicants with a copy of the applicable PTO-1449 form containing the Examiner's initials next to each reference citation.

The Present Invention

The present invention is directed to a fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain.

The Pending Claims

Claims 1-9, 12, 13, 16-28, 30-41, and 43-46 are pending and are directed to the fusion protein.

The Office Action

The Office Action has rejected claims 2-7, 9-12, 17, and 31 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Claims 1-7, 9-12, 14-19, and 28-46 have been rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description and lack of enablement. Claims 1-5, 9, 10, 14, 16-19, 32-36, and 39-45 have been rejected under 35 U.S.C. § 102 as allegedly being anticipated by WO 00/37645 (Davis et al.) ("the '645 application") and/or U.S. Patent No. 6,387,663 (Hall et al.) ("the '663 patent"). Claims 1-5, 9, 14, 17, 18, 32-34, 41, and 43-46 have been rejected under 35 U.S.C. § 103(a) for allegedly being obvious in view of Yoon et al., *Life Sciences*, *64*(16), 1435-1445 (1997) ("the Yoon reference") in combination with U.S. Patent No. 6,291,667 (Gill et al.) ("the '667 patent") and U.S. Patent 5,874,542 (Rockwell et al.) ("the '542 patent"). Reconsideration of these rejections is hereby requested.

The Amendments to the Specification and Claims

The specification has been amended to correct the misspelling of "neuropilin." Claims 1, 2, 3, 5, 6, 9, 30, 31, and 43 have been amended to point out more particularly and claim more distinctly the present invention. The amendments to claims 1 and 43 are supported by the specification at, for example, paragraph [0007], paragraph [0023], and paragraph [0045]. The amendments to claims 2, 6, and 9 are supported by the specification at, for example, paragraph [0040], paragraph [0060], paragraph [0069], and paragraph [00108]. Claim 5 has been amended to correct the dependency of that claim. Claims 3 and 30 have been amended to correct typographical errors, and claim 30 also has been amended to change its dependency. The amendment to claim 31 is supported in the specification at, for example, paragraph [0063], lines 1-7. Accordingly, no new matter has been added by way of the amendments to the claims or specification. Separate documents setting forth the precise changes to the claims and specification, as well as the text of all of the pending claims, are enclosed herewith.

Discussion of the Rejections under 35 U.S.C. § 112, second paragraph

The Office Action has rejected claims 2-7, 9-12, 17, and 31 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter of the present invention. Applicants note that claims 10 and 11 have been cancelled.

Thus, the Section 112, second paragraph, rejection will be addressed as it pertains to claims 2-7, 9, 12, 17, and 31. This rejection is traversed for the reasons set forth below.

The Office Action contends that it is not clear which flk/flt receptor is referred to in claim 2. Claim 2 has been amended to recite that the first peptide portion of the fusion proteins exhibits a higher affinity for KDR receptors than flt receptors or flk receptors. The amended claim is definite as flt or flk receptors are known in the art and one of ordinary skill in the art would appreciate that the claim is not limited to any particular flt or flk receptor.

The rejection of claims 5, 6, 9, and 31 is moot in view of the amendments to these claims, which serve merely to point out more particularly the claimed invention and do not alter the scope of the claims.

Claim 11 is rejected as being indefinite in that it is allegedly not clear what parameters are intended by "greater maturity." The specification of the present application, however, clearly sets forth the characteristics of mature blood vessels as well as methods of characterizing blood vessel maturity at, for example, paragraph [0071]. The metes and bounds of claim 11 are clear. In addition, the Office Action contends that the meaning of "dilatation" is unclear, thereby rendering claim 17 indefinite. "Dilatation" is a term commonly used in the art prior to the filing of the present application as evidenced by the definition of the term in Stedman's Medical Dictionary, 24th Ed., Williams & Wilkins, Baltimore, MD (1982) (page 397 submitted herewith). Thus, the ordinarily skilled artisan would understand the metes and bounds of claim 17.

Not Submitted

In view of the above, claims 2, 5, 6, 9, 11, 17, and 31 (and claims 3, 4, 7, 10, and 12 dependent thereon) particularly point out and distinctly claim the present invention. Applicants respectfully request withdrawal of the rejection under Section 112, second paragraph.

Discussion of the Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 1-7, 9-12, 14-19, and 28-46 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to (1) reasonably convey that the inventors had possession of the invention at the time of filing of the present application (written description) and (2) enable one of ordinary skill in the art to make and use the present invention as claimed (enablement). Due to the cancellation of claims 10, 11, 14, 15, 29, and 42, the Section 112, first paragraph, rejection will be addressed as it pertains to claims 1-7, 9, 12, 16-19, 28, 30-41, and 43-46. This rejection is traversed for the reasons set forth below.

a. Written Description and Enablement of VEGF Peptide Portion

The Office Action contends that the pending claims encompass a fusion protein comprising all functional VEGF equivalents, and that the specification does not adequately describe or enable all such possible equivalents. Claims 1 and 43, as amended, are directed to a fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion. The structure of VEGF-A peptides has been described in the art and in the present specification (see, e.g., paragraph [0007]). The specification further describes how to make and use the inventive fusion proteins employing a VEGF-A peptide portion as the first peptide portion of the fusion protein (see, e.g., the Examples).

Moreover, the specification describes the structure of various isoforms and homologs of VEGF-A peptides, including $VEGF_{121}$ (see, e.g., paragraph [0007]). In particular, the specification indicates that peptide portions that exhibit at least about 80% homology to a naturally occurring VEGF peptide portion can be used in the claimed fusion protein (see, e.g., paragraph [0023]). One of ordinary skill in the art would appreciate that a general structure is implied in a peptide portion exhibiting such a high degree of homology to a naturally occurring VEGF peptide portion. One of ordinary skill in the art would be able to isolate such homologs without undue experimentation using any one of the numerous methods described in the present specification (see, e.g., paragraphs [0014]-[0022]).

With specific reference to claim 3, the Office Action alleges that the specification does not adequately describe or enable a VEGF peptide portion with less affinity for neuropilin-1 or -2 than $VEGF_{121}$. Applicants submit that the specification discloses that the VEGF peptide portion exhibits low affinity (or no affinity) for neuropilin-1, -2, or both, as defined by a dissociation constant of preferably at least 10,000 pM (see, e.g., paragraph [0041]). Moreover, the specification describes a fusion protein comprising KAP, Ang-1, or an angiogenic fragment of either peptide in which binding with neuropilin-1 is reduced (see, e.g., paragraph [0057]). Applicants note that one of ordinary skill in the art would be able to determine protein binding affinity using routine methods known in the art (see, e.g., Wingard et al., eds., *Human Pharmacology: Molecular to Clinical*, Mosby-Year Book, Inc., St. Louis, MO (1991)).

The Office Action further alleges that VEGF is not known to have bone growth promoting activity, nor is this function described or enabled by the present specification. In particular, the Office Action contends that VEGF expression in chondrocytes is not indicative of bone growth induction by VEGF. The peptide portions of the claimed fusion protein, however, only are required to *promote* bone growth, which, Applicants submit, is a well known property of VEGF. In this regard, Ferrara et al., *Curr. Opn. Biotech.*, *11*, 617-24 (2000) (enclosed herewith), describes the near complete suppression of blood vessel invasion concomitant with

impaired trabecular bone formation when VEGF activity is inhibited. Based on these findings, the Ferrara reference concludes that VEGF-dependent blood vessels are *essential* for coupling apoptosis of hypertrophic chondrocytes with bone formation (see, e.g., page 619, left column, first complete paragraph).

b. Written Description and Enablement of Non-VEGF Peptide Portion

The Office Action contends that the specification does not adequately describe or enable all possible functional equivalents of the second non-VEGF peptide portion (see Office Action at page 7, first complete paragraph). Applicants point out that Section 112, first paragraph, I satisfied by the disclosure of a representative number of species. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one can describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a "representative number" depends on whether one of ordinary skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species, however, does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. M.P.E.P. § 2163. Moreover, if a particular claim is enabled by the specification, an Applicant need not describe all possible embodiments of that claim. M.P.E.P. § 2164.02.

The present specification discloses tens, if not hundreds, of species within the genus of angiogenesis-promoting and/or bone growth-promoting factors. The disclosed species comprise a broad spectrum of peptides that promote angiogenesis and/or bone growth, including growth factors, cytokines, signaling molecules, and transcription factors, that could be employed as the non-VEGF peptide portion of the claimed fusion protein (see, e.g., paragraphs [0048]-[0056], [0075], and [0081]). Even if there is substantial variation within the genus of factors that promote angiogenesis and/or bone growth, Applicants believe that the specification discloses a sufficient number and variety of species within the genus to reflect the variation therein.

With respect to the alleged lack of enablement, numerous methods for generating the claimed fusion proteins are described and exemplified in the present specification. Indeed, the specification discloses methods for linking the first and second peptide portions (see, e.g., paragraphs [0086]-[0092]), recombinant DNA methods for producing the fusion protein (see, e.g., paragraphs [00109]-[00117]), and viral gene transfer vectors that encode and express the fusion protein in a suitable host (see, e.g., paragraphs [00116]-[00127]). Applicants also note that methods for generating fusion proteins have been extensively described in the prior art, and such methods are referred to in the present specification. Moreover, the Examples describe

methods for generating specific fusion proteins embraced by the claims. It is urged that the disclosure of angiogenic and bone growth promoting factors in the specification and in the literature, coupled with the disclosed methods for making and using the claimed fusion protein, clearly equips the skilled artisan with the ability to practice the claimed invention using only routine methods of experimentation.

The subject matter of claims 6 and 7 allegedly is not adequately described or enabled by the present specification. Applicants note that the stability of the claimed fusion protein is described in the specification in terms of protein half-life. In this regard, paragraph [00108] discloses a range of half-lives for the fusion protein (including a half-life of at least about 10 minutes as set forth in claim 7), and specifically indicates that the claimed fusion protein exhibits a half-life at least twice as long as the half-life of an Ang-1 protein. The specification also points to specific structural features of the fusion protein, the absence or presence of which enhances protein stability. In this regard, for example, the specification discloses that removal of the Ang-1 coiled-coil domain imparts an increased half-life to a fusion protein comprising Ang-1 as the non-VEGF peptide portion (see, e.g., paragraph [0108], lines 10-14). The specification also indicates that the inclusion of cysteine residues in either or both of the VEGF and non-VEGF peptide portions of the claimed fusion protein renders the fusion protein more resistant to extracellular degradation (see, e.g., paragraph [0108], lines 14-18), thereby enhancing protein stability. Fusion protein half-life also can be extended when the non-VEGF peptide portion comprises an IgG domain, as described in the specification at paragraph [0108], lines 18-22. Methods for determining protein half-life have long been known to those skilled in the art, and include, for example, pulse-chase experiments as described in Dandri et al., *J. Virol.*, *72*, 9359-64 (1998), and Distelhorst et al., *J. Biol. Chem.*, *264*, 13080-85 (1989). Thus, Applicants submit that the subject matter of claims 6 and 7 is adequately described in the specification such that one of ordinary skill in the art would be able to make and use the present invention using only routine methods of experimentation.

The subject matter of claims 10-12 allegedly is not adequately described or enabled by the present specification. Applicants note that claims 10 and 11 have been cancelled; thus the rejection will be addressed as it pertains to claim 12. Claim 12 requires that blood vessels resulting from administration of the fusion protein are associated with more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration of endothelial cells, or any combination thereof, than blood vessels resulting from administration of a protein consisting essentially of the first peptide portion. As discussed above, disclosure of a representative number of species within a genus satisfies the written description requirement of Section 112, first paragraph. M.P.E.P. § 2163. Applicants submit that the specification discloses a representative number of species of proteins for use as the

second non-VEGF peptide portion that promote smooth muscle cell or endothelial cell proliferation (see, e.g., paragraphs [0052] and [0053]) such that one of ordinary skill in the art would understand that Applicants had possession of the claimed invention.

Moreover, methods for measuring smooth muscle cell or endothelial cell proliferation are known in the art and discussed in the specification (see, e.g., paragraphs [0070] and [0071]). It is urged that the disclosure of factors that promote proliferation of smooth muscle cells and endothelial cells in the specification and in the literature, coupled with the disclosed methods for measuring proliferation of smooth muscle and endothelial cells, clearly equips the skilled artisan with the ability to practice the claimed invention using only routine methods of experimentation.

c. Written Description and Enablement HBNF-Containing Fusion Protein

With respect to the elected species, the Office Action contends that HBNF has not been recognized in the art as exhibiting any of the characteristics recited in claims 10-12. The Office Action further contends that claim 14, when limited to the elected species, is not enabled by the present specification. Claim 15 also allegedly is not enabled by the specification.

Applicants submit that literature articles published before or shortly after the filing of the present application demonstrate that HBNF (also known as pleiotrophin (PTN) and heparin affinity regulatory peptide (HARP)) induces endothelial cell proliferation, migration, survival, and capillary-like structure formation toward a variety of endothelial cells (see, e.g., Souttou et al., *J. Cell Physiol.*, *187*, 59-64 (2001), and Papadimitriou et al., *Biochem. Biophys. Res. Comm.*, *282*, 306-313 (2001) (enclosed herewith)). Thus, claim 12 is described and enabled with respect to the elected species. The cancellation of claims 10, 11, 14, and 15 moots the Section 112, first paragraph, rejection of those claims.

The Office Action alleges that the subject matter of claim 17 is not adequately described or enabled, both generically and with respect to the elected species, HBNF. In particular, the Office Action contends that the specification does not provide guidance as to which species exhibit the functional characteristics set forth in claim 17. As discussed herein, the specification describes numerous proteins that could be employed as the second peptide portion of the claimed fusion protein, and which exhibit one or more of the functional characteristics set forth in claim 17. Indeed, such factors are disclosed in the specification at, for example, paragraph [0048], and include, for example, midkine, TNF-α, iNOS, and angiopoietin. Methods to determine if a potential second peptide portion exhibits any one of the functional characteristics set forth in claim 17 are known in the art and described extensively in the specification, as are methods for generating the claimed fusion protein. With respect to the elected species HBNF, the Office Action states that none of the properties recited in claim 17 have been reported for HBNF. Applicants respectfully disagree with this assertion, and note that claim 17 requires that

the second peptide portion exhibit any *one or combination of* the functional characteristics set forth therein. As discussed above, HBNF has been shown to promote angiogenesis by promoting endothelial cell proliferation, migration, survival, and capillary-like structure formation (see, e.g., Souttou et al., *supra*, and Papadimitriou et al., *supra)*. These references indicate that endothelial cell migration and the formation of capillary-like tubes requires degradation of the extracellular matrix. Thus, the subject matter of claim 17 encompasses HBNF, and is adequately described and enabled by the present specification.

The Office Action alleges that fusion proteins comprising VEGF and HBNF according to claim 30 are not enabled by the specification, in that one of ordinary skill in the art would not expect a soluble protein comprising HBNF to promote bone growth, wound healing, or angiogenesis of normal (i.e., non-tumor) cells. Applicants reiterate that the prior art demonstrates the angiogenesis-promoting activity of HBNF in a variety of non-tumor endothelial cell types, such as human umbilical vein endothelial cells (HUVEC), rat adrenal medulla microvascular endothelial cells (RAME), and bovine brain capillary endothelial cells (BBC). With respect to bone growth, the Office Action contends that Figure 3 of the Imai et al. reference cited by Applicants discloses inhibition of osteoblast recruitment by HBNF in a dose-dependent manner. Applicants respectfully point out that the only cells that were unresponsive to HBNF were nonosteoblastic (i.e., control) cells. Indeed, the Imai reference concludes that HBNF likely plays a role in bone formation by mediating recruitment and attachment of osteoblasts (see, e.g., page 1113, Abstract, page 1123, right column, and page 1126, left column). With respect to wound healing, Applicants submit that, while the wound healing activity of HBNF may not have been disclosed at the relevant time, such activity is an inherent feature of HBNF, as demonstrated in, for example, Deuel et al., *Arch Biochem. Biophys.*, 397, 162-171 (2002) (enclosed herewith). Accordingly, using the guidance provided by the present specification and the prior art, one of ordinary skill in the art would be able to make and use a fusion protein as set forth in claim 30.

The specification allegedly does not adequately describe and/or enable the subject matter of claims 29 and 31. Claim 29 has been cancelled, thereby mooting the written description and enablement rejections of that claim. Claim 31, as amended, requires that the second peptide portion of the fusion protein comprises an N-terminal truncated form of HBNF or MK including at least about 60% of the wild-type HBNF or MK amino acid sequence. Such truncated forms of HBNF retain the biological activity of full-length HBNF, as indicated by the Inui et al. reference cited in the present application and by the Office Action (see page 11, last complete paragraph). Thus, the subject matter of claim 31 is fully enabled by the present specification.

Finally, the Office Action contends that claims 38 and 42 are not adequately described or enabled, in that the specification does not provide guidance as to the identity of the

biological cascades associated with angiogenesis, bone growth, and wound healing (especially with respect to VEGF and HBNF), or how such cascades can be imitated. To advance prosecution of the subject application, and not in acquiescence of the rejection, claim 42 has been cancelled. Regarding claim 38, vectors comprising a polynucleotide encoding the claimed fusion protein and a second polynucleotide encoding a second protein which promotes angiogenesis, bone growth, and/or wound healing are described in the present specification at, for example, paragraph [00112]. Moreover, methods for operably linking the polynucleotide encoding the fusion protein and the second nucleotide sequence to separate promoters, such that the initiation of expression of the first nucleotide sequence and the second nucleotide sequence occurs at different times and/or in response to different factors, are described in sufficient detail at, for example, paragraph [00113]. One of ordinary skill in the art would be able to construct such vectors using the routine methods known in the art and described in the present specification (see, e.g., paragraphs [00115] – [00118]), without undue experimentation.

Therefore, in view of the foregoing, the claims are sufficiently supported, adequately described, and fully enabled by the present specification. As such, the rejection under Section 112, first paragraph, is improper and should be withdrawn.

Discussion of the Rejections under 35 U.S.C. § 102

Claims 1-4, 9, 10, 14, 16-19, 32-34, 39, 40, and 43-45 have been rejected under Section 102(a) as allegedly being anticipated by the '645 application. Claims 1-5, 9, 14, 17, 18, 32-36, and 39-42 have been rejected under Section 102(e) as allegedly being anticipated by the '663 patent. These rejections are traversed for the reasons set forth below.

With respect to the Section 102(a) rejection, Applicants note that claims 10 and 14 have been cancelled. Thus, this rejection will be addressed as it pertains to claims 1-4, 9, 16-19, 32-34, 39, 40, and 43-45. The Office Action contends that the '645 application discloses fusion proteins comprising the receptor binding domains of two ligands, including a fusion protein comprising the receptor binding domains of VEGF and angiopoietin (Ang-1). Applicants note that claims 1 and 43, as amended, are directed to a fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions *separately* promote angiogenesis, bone growth, and/or wound healing. Applicants submit that the angiopoietin peptide portion of the disclosed VEGF-Ang-1 fusion protein does not separately promote angiogenesis or bone growth. In this respect, the '645 application discloses a fusion protein comprising the receptor binding domains of VEGF and Ang-1

linked by a multimerizing domain, which enables "clustering" of the Ang-1 receptor binding domain. The '645 application indicates that Ang-1 "clustering" induces or enhances its biological activity (see, e.g., page 8, lines 9-24). Indeed, the '645 application discloses that monomeric Ang-1 has low affinity for the Tie-2 receptor, as compared to highly clustered (e.g., tetrameric) VEGF-Ang-1 fusion proteins.

Therefore, contrary to the assertion of the Office Action, the non-VEGF peptide portion of the fusion protein disclosed in the '645 application does not separately promote angiogenesis, bone growth, and/or wound healing, as required by claims 1 and 43, but rather requires multimerization to exert its biological activity. Thus, claims 1-4, 9, 16-19, 32-34, 39, 40, and 43-45 define novel, as well as unobvious, subject matter in view of the '645 application. Accordingly, the Section 102(a) rejection should be withdrawn.

With respect to the Section 102(e) rejection, Applicants note that claims 14 and 42 have been cancelled. Thus, this rejection will be discussed as it pertains to claims 1-5, 9, 17, 18, 32-36, and 39-41. The Office Action alleges that the '663 patent discloses a fusion protein comprising a VEGF and von Willebrand factor (vWF), which is considered in the art to be an angiogenic factor as defined by the present specification. Applicants note that claims 1 and 43 require that the second peptide portion lack a collagen binding domain. The '663 patent does not disclose or suggest constructing a fusion protein comprising a VEGF and a second non-VEGF peptide that lacks a collagen binding domain. On the contrary, the disclosed fusion proteins contain an angiogenesis modulating agent (e.g., VEGF) linked to a polypeptide encoding a collagen binding domain (CBD) (e.g., the CBD of vWF). Thus, the '663 patent does not disclose or suggest the subject matter of claim 1, or claims depending therefrom. As such, claims 1-5, 9, 17, 18, 32-36, and 39-41 define novel, as well as unobvious, subject matter in view of the '663 patent, and the Section 102(e) rejection should be withdrawn.

Discussion of the Rejections under 35 U.S.C. § 103(a)

Claims 1-5, 9, 14, 17, 18, 32-34, 41, and 43-46 have been rejected under Section 103(a) for allegedly being unpatentable over the Yoon reference in view of the '667 patent and the '542 patent. The rejection will be addressed as it pertains to claims 1-5, 9, 17, 18, 32-34, 41, and 43-46 in view of the cancellation of claim 14. This rejection is traversed for the reasons set forth below.

According to the Office Action, the Yoon reference discloses EGF-angiogenin fusion proteins that target tumor cells via EGF receptors, and kill tumor cells via internalization of the angiogenin portion of the fusion protein. The '667 patent allegedly discloses the presence of VEGF receptors on Kaposi's sarcoma cells, and that Kaposi sarcoma cell survival depends

on VEGF. The '542 patent allegedly discloses high levels of flk-1 receptor expression in glioblastoma-associated endothelial cells. The Office Action contends that one of ordinary skill in the art would have been motivated by the '667 patent and the '542 patent to substitute VEGF for EGF in the fusion protein disclosed by the Yoon reference for the purpose of killing Kaposi's sarcoma or glioblastoma cells, thereby arriving at the presently claimed fusion protein.

Prior to the filing of the present application, one of ordinary skill in the art was well aware of the role that angiogenesis plays in promoting tumor growth, survival, and metastasis (see, e.g., Kerbel, *Carcinogenesis*, *21*, 505-15 (2000)). Moreover, as described in the present specification, the angiogenic properties of VEGF, including its role in tumor angiogenesis, were well known before the filing of the present application (see, e.g., Schlaeppi et al., *Cancer Metastasis Rev.*, *18*, 473-81 (1999), and Ferrara, *Breast Cancer Res. Treat.*, *36*, 127-37 (1995)). Therefore, in order to kill tumor cells, one of ordinary skill in the art would not provide tumor cells with an agent that *promotes* tumor angiogenesis, such as VEGF. Furthermore, the '667 patent and the '542 patent arguably teach away from the present invention. In this respect, the '667 patent discloses methods to induce tumor cell cytotoxicity by inhibiting production of, or signaling by, VEGF, while the '542 patent discloses the use of monoclonal antibodies to neutralize VEGF to inhibit angiogenesis. As such, one of ordinary skill in the art seeking to kill tumor cells would not have been motivated by the '667 patent or the '542 patent to substitute a VEGF for EGF in the fusion protein disclosed by the Yoon reference, inasmuch as the VEGF peptide portion would enhance tumor cell survival by promoting tumor angiogenesis.

Thus, the subject matter of claims 1-5, 9, 17, 18, 32-34, 41, and 43-46 is unobvious over the Yoon reference, the '667 patent, and the '542 patent, when considered alone or in combination. Accordingly, the Section 103 rejection is improper and should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: February 24, 2003

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: 2/24/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kovesdi et al.

Application No. 09/832,355

Filed: April 10, 2001

For: VEGF FUSION PROTEINS

Art Unit: 1647

Examiner: Spector, L.

AMENDMENTS TO SPECIFICATION AND CLAIMS MADE IN RESPONSE TO OFFICE ACTION DATED OCTOBER 23, 2002

Amendments to paragraph [0041]:

The VEGF peptide portion also desirably exhibits low affinity for [neurophilin] neuropilin-1, [neurophilin] neuropilin-2, or both. Preferably, the VEGF peptide portion exhibits an affinity for either or both [neurophilins] neuropilins or related proteins (analogs or variants), e.g., marked by a dissociation constant of at least 1,000 pM, more preferably at least 10,000 pM. Ideally, the VEGF peptide portion exhibits an affinity for [neurolipin] neuropilin-1 and [neurolipin] neuropilin-2 equal to, or less than, the affinity exhibited by $VEGF_{121}$ (i.e., no apparent affinity). By exhibiting low affinity, or, more preferably, by not binding [neurophilins] neuropilins whatsoever, the VEGF peptide portion can avoid undesired interactions which reduce the amount of binding to therapeutic receptors of interest (e.g., the KDR receptor) and avoids interaction with [neurophilin] neuropilin-associated tumor cells.

Amendments to paragraph [0057]:

More preferably, the second peptide portion comprises KAP, Ang-1, or an angiogenic fragment of either peptide (preferably a fragment which binds the TIE-2 receptor). Fragments of Ang-1, lacking a significant portion of the N-terminus of Ang-1 are also preferred. Desirably, such truncated Ang-1 peptide portions comprise less than about 50%, more preferably less than about 60%, of the Ang-1 amino acid sequence. Preferably, the Ang-1 truncated peptide portion is truncated in the N-terminal portion of the Ang-1 amino acid sequence. Truncated Ang-1 peptide portions lacking all or part of the predicted Ang-1 alpha helix rich coiled coil domain (SEQ ID NO: 18) (e.g., at least 10%, preferably at least about 50%, and more preferably at least about 90% of either the C-terminus or N-terminus of the domain, or both) are also desirable (other predicted coiled coil domains, including

possible Ang-1 coiled coil domains are discussed further herein), as are Ang-1 peptide portions lacking the variable N-terminal domain (SEQ ID NO: 19) (similar modifications can be applied to other angiopoietin peptide portions and angiopoietin related factor peptide portions). Fusion proteins including such truncated Ang-1, or, more preferably, KAP peptide portions, may permit better binding to the KDR and TIE-2 receptors. Fusion proteins that exhibit higher affinity for both the KDR and TIE-2 receptors over full length VEGF-Ang-1 homologs are preferred. Moreover, due to the non-heparin binding nature of the preferred VEGF peptide portion, binding with undesired receptors (e.g., [neurophilin] neuropilin-1) is reduced, thereby increasing TIE-2/KDR interaction.

Amendments to paragraph [0083]:

As indicated above, in some contexts a fusion protein consisting of a heparin-binding VEGF peptide portion is preferred over fusion proteins comprising a non-heparin-binding VEGF peptide portion. Accordingly, such fusion proteins also are provided by the invention. In general, the principles applicable to the non-heparin-binding VEGF peptide portion are also applicable to such heparin-binding VEGF peptide portions, except with respect to factors such as mobility (discussed with respect to non-heparin-binding VEGF fusion proteins below), pH (as discussed above), and/or protein interactions (e.g., [neurophilin] neuropilin interactions or VEGF receptor interactions), which typically will vary from those described above with respect to non-heparin-binding VEGF peptide portions (i.e., by exhibiting biological activity similar to heparin-binding VEGFs, such as $VEGF_{189}$ or $VEGF_{165}$). The heparin-binding VEGF peptide portion can comprise any suitable heparin-binding VEGF (e.g., a $VEGF_{189}$ or homolog thereof). $VEGF_{165}$, heparin-binding fragments thereof, and homologs thereof, are preferred wild-type and wild-type-derived heparin binding VEGF peptide portions components. Other advantageous heparin-binding VEGFs include VEGFs derived from $VEGF_{121}$, which typically generated through addition of the heparin-binding domain of another VEGF, such as $VEGF_{189}$ or an artificial heparin-binding domain. Examples of such VEGFs include $VEGF_{121.2}$ (SEQ ID NO: 60) and $VEGF_{121.3}$ (SEQ ID NO: 61), which include a heparin binding domain derived from $VEGF_{189}$, and $VEGF_{121.5}$ (SEQ ID NO: 62) and $VEGF_{121.6}$ (SEQ ID NO: 63), which include artificial heparin binding domains. Such VEGFs may exhibit higher heparin binding than $VEGF_{165}$ and, thus, can be advantageous in aspects where a heparin binding VEGF peptide portion is desirable. Similar modified heparin-binding VEGFs, which also can be suitable for incorporation in such fusion proteins, are described in International Patent Application WO 98/36075.

Amendments to existing claims:

1. (Amended) A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain.

2. (Amended) The fusion protein of claim 1, wherein the first peptide portion comprises a VEGF-A peptide portion which exhibits a higher affinity for KDR receptors than flt receptors or flk receptors [the flt/flk receptors].

3. (Amended) The fusion protein of claim 2, wherein the VEGF-A peptide portion exhibits about equal [of] or less affinity for [neurophilin] neuropilin-1, [neurophilin] neuropilin-2, or both, as $VEGF_{121}$.

5. (Amended) The fusion protein of claim [4] 1, wherein the first peptide portion comprises $VEGF_{121}$.

6. (Amended) The fusion protein of claim 1, wherein the fusion protein has a half-life in a mammalian host at least twice as long as the half-life of a protein consisting essentially of either the first peptide portion[,] and/or at least twice as long as the half-life of a protein consisting essentially of the second peptide portion[, or both].

9. (Amended) The fusion protein of claim 1, wherein the fusion protein is more angiogenic than a protein consisting essentially of [either] the first peptide portion[,] and/or is more angiogenic than a protein consisting essentially of the second peptide portion[, or both].

[10. The fusion protein of claim 9, wherein blood vessels resulting from administration of the fusion protein to a mammalian host have less permeability than blood vessels resulting from administration of a protein consisting essentially of the first peptide portion.]

[11. The fusion protein of claim 9, wherein blood vessels resulting from administration of the fusion protein to a mammalian host exhibit greater maturity than blood

vessels resulting from administration of a protein consisting essentially of the first peptide portion.]

[14. The fusion protein of claim 1, wherein the fusion protein diffuses through the extracellular matrix in a mammalian host upon administration to a mammalian host from a point of administration, the cell in which it is expressed, or both, farther than a protein consisting essentially of a naturally occurring heparin-binding form of a VEGF.]

[15. The fusion protein of claim 14, wherein the fusion protein diffuses through the extracellular matrix in a mammalian host upon administration to a mammalian host from a point of administration, the cell in which it is expressed, or both, farther than a protein consisting essentially of the second peptide portion.]

[29. The fusion protein of claim 28, wherein the second peptide portion comprises a peptide that is about 30% or more homologous to HBNF or MK.]

30. (Amended) The fusion protein of claim 29, wherein the second peptide portion comprises HBNF or MK, or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or a combination thereof.

31. (Amended) The fusion protein of claim 30, wherein the second peptide portion comprises an N-terminal truncated form of HBNF or MK[, and the truncated form comprises] including at least about 60% [or less] of the wild-type HBNF or MK amino acid sequence.

[42. A method of producing a fusion protein comprising introducing the vector of claim 38 into a cell and permitting or inducing expression of the first nucleotide sequence and the second nucleotide sequence in a manner which imitates a biological cascade associated with angiogenesis, bone growth, or wound healing.]

43. (Amended) A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis, bone growth, wound healing, or any combination thereof, wherein the VEGF peptide portion is at least about 115 amino acids in length [or] and the second peptide portion lacks a collagen binding domain.